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(54) **Magnesium salt of the (-)-enantiomer of omeprazole and its use**

Magnesiumsalz des (-)-Enantiomers von Omeprazol und dessen Verwendung

Sel de magnésium de l'énantiomère (-) d'omeprazole et son utilisation

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(56) References cited:
EP-A- 0 124 495 **DE-A- 4 035 455**

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Description

Field of the invention

[0001] The present invention is directed to new compounds with high optical purity, their use in medicine and their use in the manufacture of pharmaceutical preparations.

Background of the invention

[0002] The compound 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole, having the generic name omeprazole, and therapeutically acceptable alkaline salts thereof are described in EP 5129 and EP 124 495, respectively, Omeprazole and its alkaline salts are effective gastric acid secretion inhibitors, and are useful as antiulcer agents. The compounds, being sulfoxides, have an asymmetric center in the sulfur atom, i.e. exist as two optical isomers (enantiomers). It is desirable to obtain compounds with improved pharmacokinetic and metabolic properties which will give an improved therapeutic profile such as a lower degree of interindividual variation. The present invention provides such compounds, which are novel salts of single enantiomers of omeprazole.

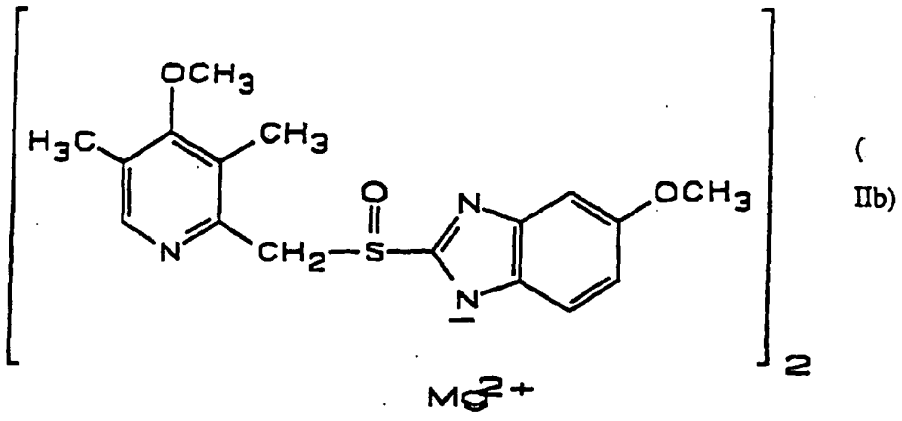
[0003] The separation of the enantiomers of omeprazole in analytical scale is described in e.g. J. Chromatography, 532 (1990), 305-19 and in a preparative scale in DE 4035455. The latter has been done by using a diastereomeric ether which is separated and thereafter hydrolysed in an acidic solution. Under the acidic conditions needed for hydrolysis of the attached group, omeprazole is quite sensitive and the acid has to be quickly neutralized with a base to avoid degradation of the acid-sensitive compound. In the above mentioned application this is done by adding the reaction mixture containing concentrated sulfuric acid to a concentrated solution of NaOH. This is disadvantageous because there is a great risk of locally reaching pH values between 1-6, which would be devastating for the substance. Moreover, instantaneous neutralisation will create heat which will be difficult to handle in large scale production.

[0004] The present invention in a further aspect provides a novel method for preparing the novel compounds of the invention in large scale. This novel method can also be used in large scale to obtain single enantiomers of omeprazole in neutral form.

[0005] There is no example known in the prior art of any isolated or characterized salt of optically pure omeprazole, i.e. single enantiomers of omeprazole neither of any isolated or characterized salt of any optically pure omeprazole analogue.

Detailed description of the invention

[0006] The present invention refers to new optically pure magnesium salts of omeprazole according to compound IIb



(IIb)

IIb (-)-enantiomer

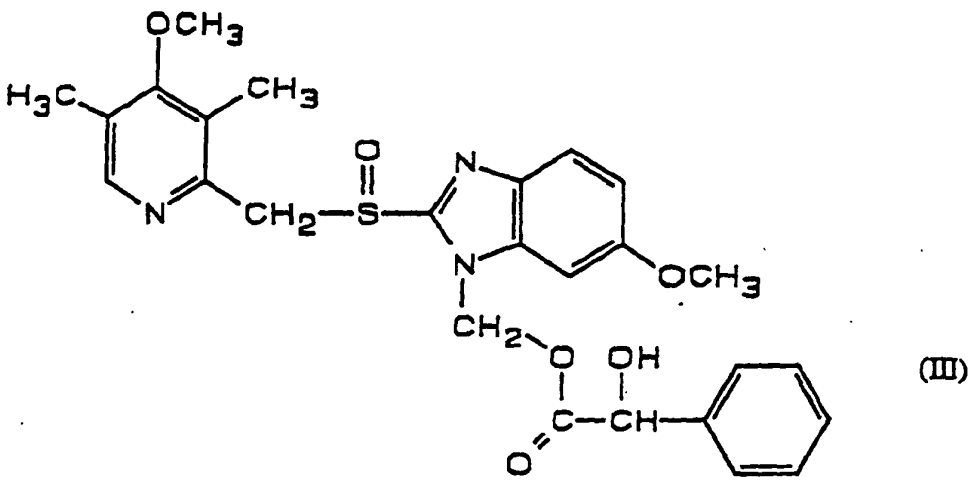
[0007] According to the invention there is provided a magnesium salt of (-)-omeprazole with an optical purity of ≥ 99.8% e.e. and the use of such a salt for the manufacture of a medicament for the inhibition of gastric acid secretion.

[0008] Single enantiomers of omeprazole have hitherto only been obtained as syrups and not as crystalline products. By means of the novel specific method according to one aspect of the invention of preparing the single enantiomers of omeprazole, the salts defined by the present invention are easy to obtain. In addition, the salts, however not the neutral forms, are obtained as crystalline products. Because it is possible to purify optically impure salts of the enantiomers of omeprazole by crystallisation, they can be obtained in very high optical purity, namely ≥99.8% enantiomeric excess (e.e.) even from an optically contaminate preparation. Moreover, the optically pure salts are stable towards racemization both in neutral pH and basic pH, which was surprising since the known deprotonation at the carbon atom between the pyridine ring and the chiral sulphur atom was expected to cause racemization under alkaline conditions. This high stability towards racemization makes it possible to use a single enantiomeric salt of the invention in therapy.

[0009] The specific method of preparation of the single enantiomers of omeprazole is also disclosed herein and can be used to obtain the single enantiomers of omeprazole in neutral from as well as the salts thereof.

[0010] The compounds according to the invention may be used for inhibiting gastric acid secretion in mammals and man. In a more general sense, the compounds of the invention may be used for the treatment of gastric acid-related diseases and gastrointestinal inflammatory diseases in mammals and man, such as gastric ulcer, duodenal ulcer, reflux esophagitis, and gastritis. Furthermore, the compounds may be used for treatment of other gastrointestinal disorders where gastric antisecretory effect is desirable e.g. in patients on NSAID therapy, in patients with gastrinomas, and in patients with accute upper gastrointestinal bleeding. They may also be used in patients in intensive care situations, and pre- and postoperatively to prevent acid aspiration and stress ulceration. The compound of the invention may also be used for treatment or prophylaxis of inflammatory conditions in mammals, including man, especially those involving lysozymal enzymes. Conditions that may be specifically mentioned are rheumatoid arthritis and gout. The compound of the invention may also be useful in the treatment of psoriasis as well as in the treatment of Helicobacter infections.

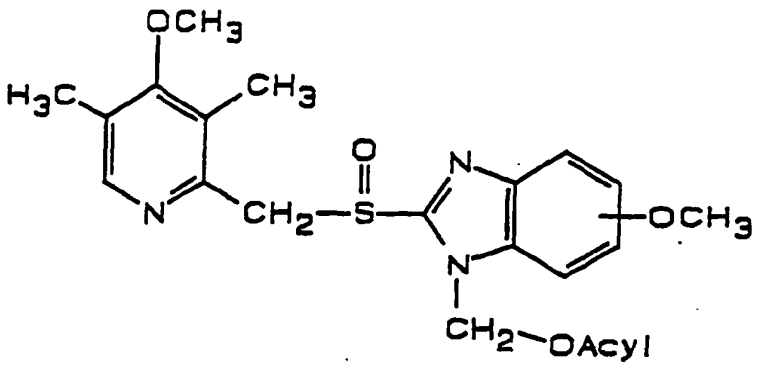
[0011] Compound III is an intermediate used in the specific method of preparation.



(III)

Preparation

[0012] The optically pure compounds of the invention, i.e. the single enantiomers, are prepared by separating the two stereoisomers of a diastereomeric mixture of the following type, 5- or 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl) methyl]sulfinyl]-1-[acyloxymethyl]-1H-benzimidazole, formula IV



(IV)

wherein the methoxy substituent in the benzimidazole moiety is in position 5 or 6, and wherein the Acyl radical is as defined below, followed by a solvolysis of each separated diastereomer in an alkaline solution. The formed single enantiomers of omeprazole are then isolated by neutralizing aqueous solutions of the salts of the single enantiomers of omeprazole with a neutralizing agent which can be an acid or an ester such as methyl formate.

[0013] The Acyl moiety in the diastereomeric ester may be a chiral acyl group such as mandeloyl, and the asymmetric center in the chiral acyl group can have either R or S configuration.

[0014] The diastereomeric esters can be separated either by chromatography or fractional crystallization.

[0015] The solvolysis usually takes place together with a base in a protic solvent such as alcohols or water, but the acyl group may also be hydrolysed off by a base in an aprotic solvent such as dimethylsulfoxide or dimethylformamide. The reacting base may be OH^- or R^1O^- where R^1 can be any alkyl or aryl group.

[0016] To obtain the optically pure Na^+ salts, i.e. the single enantiomers of omeprazole Na^+ salts, the resulting compound is treated with a base, such as NaOH, in an aqueous or nonaqueous medium, or with $NaOR^2$ wherein R^2 is an alkyl group containing 1-4 carbon atoms, or with $NaNH_2$. Also alkaline salts wherein the cation is Li^+ or K^+ may be prepared using lithium or potassium salts of the above mentioned bases. In order to obtain the crystalline form of the Na^+ salt, addition of NaOH in a non-aqueous medium such as a mixture of 2-butanone and toluene, is preferred.

[0017] To obtain the optically pure Mg^{2+} salts of the invention, optically pure Na^+ salts are treated with an aqueous solution of an inorganic magnesium salt such as $MgCl_2$, whereupon the Mg^{2+} salts are precipitated. The optically pure Mg^{2+} salts may also be prepared by treating single enantiomers of omeprazole with a base, such as $Mg(OR^3)_2$, wherein R^3 is an alkyl group containing 1-4 carbon atoms, in a non-aqueous solvent such as alcohol (only for alcoholates), e.g. ROH, or in an ether such as tetrahydrofuran. In an analogous way, also alkaline salts wherein the cation is Ca^{2+} can be prepared, using an aqueous solution of an inorganic calcium salt such as $CaCl_2$.

[0018] For clinical use the single enantiomers, i.e. the optically pure compounds, of the invention are formulated into pharmaceutical formulations for oral, rectal, parenteral or other modes of administrations. The pharmaceutical formulations contain the single enantiomers of the invention normally in combination with a pharmaceutically acceptable carrier. The carrier may be in form of a solid, semisolid or liquid diluent, or capsule. These pharmaceutical preparations are a further object of the invention. Usually the amount of active compound is between 0.1-95% by weight of the preparation, between 0.2-20% by weight in preparations for parenteral use and between 1-50% by weight in preparations for oral administration.

[0019] In the preparation of pharmaceutical formulations in form of dosage units for oral administration the optically pure compound may be mixed with a solid, powdered carrier, such as lactose, saccharose, sorbitol, mannitol, starch, amylopectin, cellulose derivates, gelatin or another suitable carrier, stabilizing substances such as alkaline compounds e.g. carbonates, hydroxides and oxides of sodium, potassium, calcium, magnesium and the like as well as with lubricating agents such as magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethylenglycol waxes. The mixture is then processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalysed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-forming polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different amounts of the active compound present.

[0020] Soft gelatine capsules may be prepared with capsules containing a mixture of the active compound, vegetable oil, fat, or other suitable vehicle for soft gelatine capsules. Soft gelatine capsules may also be enteric-coated as described above.

[0021] Hard gelatine capsules may contain granules or enteric-coated granules of the active compound. Hard gelatine

capsules may also contain the active compound in combination with a solid powdered carrier such as lactose, saccharose, sorbitol, mannitol, potato starch, amylopectin, cellulose derivates or gelatin. The capsules may be enteric-coated as described above.

[0022] Dosage units for rectal administration may be prepared in the form of suppositories which contain the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatine rectal capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatine rectal capsules, or they may be prepared in the form of a ready-made micro enema, or they may be prepared in the form of a dry micro enema formulation to be reconstituted in a suitable solvent just prior to administration.

[0023] Liquid preparation for oral administration may be prepared in the form of syrups or suspensions, e.g. solutions or suspensions containing from 0.2% to 20% by weight of the active ingredient and the remainder consisting of sugar or sugar alcohols and a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharine and carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of dry powder to be reconstituted with a suitable solvent prior to use.

[0024] Solutions for parenteral administrations may be prepared as solutions of the optically pure compounds of the invention in pharmaceutically acceptable solvents, preferably in a concentration from 0.1 to 10% by weight. These soultions may also contain stabilizing agents and/or buffering agents and may be manufactured in different unit dose ampoules or vials. Solutions for parenteral administration may also be prepared as dry preparations to be reconstituted with a suitable solvent extemporaneously before use.

[0025] The typical daily dose of the active compound will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, oral and parenteral dosages will be in the range of 5 to 500 mg per day of active substance.

[0026] The invention is illustrated by the following examples.

Example 1. Preparation of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole magnesium salt

[0027]

A. (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole sodium salt (0.165 g, 0.45 mmol) was dissolved in water (3 ml). To this mixture 2 ml of an aqueous solution of $MgCl_2xH_2O$ (46 mg, 0.23 mmol) was added dropwise and the formed precipitate was isolated by centrifugation. There was obtained mg (51%) of the product as a white powder. The optical purity (ee) of the product was 99.9% which was the same or better as the optical purity of the starting material. The optical purity was determined by chromatography on an analytical chiral column. $[\alpha]_D^{20}$=-128°(c=1%, methanol).

B. The starting compound of Example 1A, i.e. the (+)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole sodium salt, was prepared as follows.

100 mg (0.3 mmol) of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole (contaminated with 3% of the (+)-isomer) was dissolved in 1 ml of 2 butanone with stirring. 60 µl of an aqueous solution of 5.0 M sodium hydroxide and 2 ml of toluene were added. The resultant mixture was nonhomogeneous. In order to obtain a clear solution, more 2-butanone was added (ca 1 ml) and the mixture was stirred at ambient temperature over night. The formed precipitate was filtered off and washed with ether. There was obtained 51 mg (46%) of the title compound as white crystals m.p. (decomposition) 246-248°C. The optical purity (e.e) which was analyzed by chiral column chromatography was ≥99.8%. $[\alpha]_D^{20}$= +42,8°(c=0.5%, water). NMR data are given below (1B).

C. The starting compound of Example 1B, i.e. the (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazole, was prepared as follows.

0.23 g (0.45 mmol) of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole was dissolved in 15 ml methanol. A solution of 36 mg (0.9 mmol) sodium hydroxid in 0.45 ml water was added, and after 10 minutes the mixture was evaporated on a rotavapor. The residue was partitioned between 15 ml water and 15 ml dichloromethane. The organic solution was extracted with 15 ml water and to the combined aqueous solutions was added 85 µl (1.4 mmol) methyl formate. After 15 minutes the mixture was extracted with 3x10 ml dichloromethane. The organic solution was dried over Na_2SO_4 and then evaporated There was obtained 0.12 g (77%) of the title compound as a colourless syrup. The optical purity (e.e.) which was analyzed by chiral column chromatography was 94%. $[\alpha]_D^{20}$= -155°(c=5%, chloroform). NMR data are given below (1C). The preparation of the starting compound of Example 1C is described in Example 2B.

Ex. Solvent	NMR data δppm
1B. DMSO-D_6 500 MHz	2.20 (s,3H), 2.22 (s,3H), 3.69 (s, 3H), 3.72 (s, 3H), 4.37 (d, 1H), 4.75 (d, 1H), 6.54 (dd, 1H), 6.96 (d, 1H) 7.30 (d, 1H), 8.21 (s, 1H).
1C. $CDCl_3$ 300 MHz	2.18, (s, 3H), 2.22 (s, 3H), 3.68 (s, 3H), 3.83 (s, 3H), 4.77 (m, 2H), 6.93 (dd, 1H), ≈7.0 (b, 1H), ≈7.5 (b, 1H), 8.19 (s, 1H).

Preparation of the synthetic intermediates according to the invention will be described in the following examples.

Example 2

A. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2 pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

[0028] A solution of 3.4 g sodium hydroxide in 40 ml water was added to a mixture of 14.4 g (42 mmol) tetrabutylammonium hydrogen sulphate and 6.4 g (42 mmol) (R)-(-)-mandelic acid. The mixture was extracted with 400 ml chloroform After separation, the organic extract was heated to reflux with 16.6 g (42 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole. Evaporation of the solvent was followed by dilution with 100 ml dichloromethane and 700 ml ethyl acetate. The mixture was washed with 3 x 200 ml water and the organic solution was dried over $MgSO_4$ and then evaporated. The crude material was purified by recrystallization from 100 ml acetonitrile, giving 8.1 g of the title compound (38%) as a diastereomeric mixture.
[0029] NMR data are given below (2A).

B. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(R)-mandeloyloxymethyl]-1H-benzimidazole

[0030] The diastereomers of the title compound of A above were separated using reversed phase chromatography (HPLC). Approximately 300 mg of the diastereomeric mixture was dissolved in 10 ml hot acetonitrile which was diluted with 10 ml of a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The solution was injected to the column and the compounds were eluted with a mixture of aqueous 0.1 M ammoniumacetate and acetonitrile (70/30). The more hydrophilic isomer was easier to obtain pure than the less hydrophilic one. The work up procedure for the fraction which contained pure isomer was as follows; extraction with dichloromethane, washing the organic solution with aqueous 5 % sodium hydrogen carbonate solution, drying over Na_2SO_4 and evaporation of the solvent on a rotavapor (at the end of the evaporation the removal of acetonitrile was facilitated by adding more dichloromethane). Using 1.2 g of the diastereomeric mixture with the above mentioned technique, the more hydrophilic isomer, 410 mg, was obtained in a pure state as a colourless syrup.
[0031] NMR data are given below (2B).

Example 3

A. Preparation of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

[0032] The product was obtained from 8.1 g (202 mmol) sodium hydroxide in 100 ml water, 34.4 g (101 mmol) tetrabutylammonium hydrogen sulfate, 15.4 g (101 mmol) (S)-(+)-mandelic acid and 39.9 g (101 mmol) of the racemate of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1-[chloromethyl]-1H-benzimidazole using the same procedure as in Example 2A. Recrystallization from 100 ml acetonitrile yielded 21.3 g, i.e. 41% of the title compound as a diastereomeric mixture.
[0033] NMR data are given below (3A).

B. Separation of the more hydrophilic diastereomer of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloyloxymethyl]-1H-benzimidazole

[0034] The diastereomers of the title compound of A above were separated using reversed phase chromatography (HPLC) in the same way as in Example 2B, but using the diasteromeric mixture of 6-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-(R/S)-sulfinyl]-1-[(S)-mandeloloxymethyl]-1H-benzimidazole instead of the (R)-mandelic ester used

in Example 2B. Using 2.1 g of the diastereomeric mixture, the more hydrophilic isomer, 760 mg, was obtained in a pure state as a colourless syrup.

[0035] NMR data are given below (3B).

Ex.	Solvent	NMR data δ ppm
2A.	$CDCl_3$ 500 MHz	2.18 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.95-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s, 1H).
2B.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 5.35 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 7.37 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).
3A.	$CDCl_3$ 500 MHz	2.19 (s, 3H), 2.20 (s, 3H), 2.36 (s, 3H), 2.39 (s, 3H), 3.77 (s, 3H), 3.78 (s, 3H), 3.83 (s, 3H), 3.87 (s, 3H), 4.80 (d, 1H), 4.88 (d, 1H), 5.0 (m, 2H), 5.34 (s, 2H), 6.43 (d, 1H), 6.54 (d, 1H), 6.6-6.7 (m, 2H), 6.90 (d, 1H), 6.96-6.98 (m, 2H), 7.01 (d, 1H), 7.2-7.3 (m, 6H), 7.37 (m, 2H), 7.44 (m, 2H), 7.58 (d, 1H), 7.62 (d, 1H), 7.95 (s, 1H), 7.97 (s.1H).
3B.	$CDCl_3$ 500 MHz	2.20 (s, 3H), 2.36 (s, 3H), 3.78 (s, 3H), 3.82 (s, 3H), 4.80 (d, 1H), 5.00 (d, 1H), 535 (d, 1H), 6.43 (d, 1H), 6.63 (d, 1H), 6.90 (d, 1H), 6.97 (dd, 1H), 7.2-7.3 (m, 3H), 737 (m, 2H), 7.62 (d, 1H), 7.97 (s, 1H).

Stability towards racemization at different pH:es

[0036] The stability of the optically pure compound of the invention towards racemization has been measured at low concentrations in refrigerator in aqueous buffer solutions at pH 8, 9.3, 10 and 11.2. The stereochemical stability was measured by comparing the optical purity for the (-)-isomer of 5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole in buffer solution immediately after dissolving and after several days. The measurement was performed by chromatography on an analytical chiral column. The surprising high stereochemical stability in alkaline conditions for the compound of the invention is exemplified by the fact that no racemization for the test compound was obtained at pH 11.2 even after 21 days. At pH 8,9.3 and 10, the chemical degradation of the compound is more apparent which makes the racemization measurement more difficult to perform, however at none of these pH values a detectable racemization was obtained after 16 days.

Claims

1. The use of a magnesium salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazole ((-)-omeprazole) with an optical purity of ≥ 99.8% enantiomeric excess (e.e.) for the manufacture of a medicament for the inhibition of gastric acid secretion.

2. The use as claimed in Claim 1 wherein the salt is crystalline.

3. The use as claimed in Claim 1 or Claim 2 wherein medicament is for the treatment of a gastric acid-related disease and/or a gastrointestinal inflammatory disease.

4. The use as claimed in Claim 3 wherein the disease is a gastric ulcer, a duodenal ulcer, reflux esophagitis or gastritis.

5. The use as claimed in Claim 4 wherein the disease is reflux esophagitis.

6. The use as claimed in Claim 1 or Claim 2 wherein the patient is on NSAID therapy, has a gastrinoma and/or has acute upper gastrointestinal bleeding.

7. The use as claimed in Claim 1 or Claim 2 wherein the medicament is for the treatment of a patient in an intensive care situation and/or is to be used pre- and postoperatively to prevent acid aspiration and stress ulceration.

8. The use as claimed in Claim 1 or Claim 2 wherein the medicament is used in the treatment of a *Helicobacter* infection.

9. A magnesium salt of (-)-5-methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)-methyl]sulfinyl]-1H-benzimidazole ((-)-omeprazole) with an optical purity of ≥ 99.8% enantiomeric excess (e.e.).

10. A salt as claimed in Claim 9 for use in therapy.

11. A salt as claimed in Claim 10 for use in the treatment or prophylaxis of a condition as defined in any one of Claims 3 to 8.

12. A salt as claimed in any one of Claims 9 to 11 which is crystalline.

13. A pharmaceutical composition of a salt as claimed in any one of Claims 9 to 12 together with a pharmaceutically acceptable carrier.

Patentansprüche

1. Verwendung eines Magnesiumsalzes von (-)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]sulfinyl]-1H-benzimidazol ((-)-Omeprazol) mit einer optischen Reinheit von ≥ 99,8% Enantiomerenüberschuss (e.e.) zur Herstellung eines Medikaments für die Hemmung der Magensäuresekretion.

2. Verwendung, wie sie im Anspruch 1 beansprucht wird, wobei das Salz kristallin ist.

3. Verwendung, wie sie im Anspruch 1 oder im Anspruch 2 beansprucht wird, wobei das Medikament zur Behandlung einer mit der Magensäure im Zusammenhang stehenden Erkrankung und/oder einer entzündlichen gastrointestinalen Erkrankung gedacht ist.

4. Verwendung, wie sie im Anspruch 3 beansprucht wird, wobei die Erkrankung ein Magengeschwür, ein Zwölffingerdarmgeschwür, eine Refluxösophagitis oder eine Gastritis ist.

5. Verwendung, wie sie im Anspruch 4 beansprucht wird, wobei die Erkrankung eine Refluxösophagitis ist.

6. Verwendung, wie sie im Anspruch 1 oder im Anspruch 2 beansprucht wird, wobei der Patient einer NSAID-Therapie unterzogen wird, ein Gastrinom hat und/oder akute obere gastrointestinale Blutungen hat.

7. Verwendung, wie sie im Anspruch 1 oder im Anspruch 2 beansprucht wird, wobei das Medikament zur Behandlung eines Patienten, der einer Intensivbehandlung unterzogen wird, gedacht ist und/oder es pro- und postoperativ zur Verhinderung einer Säureaspiration und Stressulkus-Entstehung verwendet werden soll.

8. Verwendung, wie sie im Anspruch 1 oder im Anspruch 2 beansprucht wird, wobei das Medikament bei der Behandlung einer Helicobacter-Infektion eingesetzt wird.

9. Magnesiumsalz von (-)-5-Methoxy-2-[[(4-methoxy-3,5-dimethyl-2-pyridinyl)methyl]-sulfinyl]-1H-benzimidazol ((-) Omeprazol) mit einer optischen Reinheit von ≥ 99,8% Enantiomerenüberschuss (e.e.).

10. Salz, wie es im Anspruch 9 beansprucht wird, für die Verwendung in der Therapie.

11. Salz, wie es im Anspruch 10 beansprucht wird, für die Verwendung bei der Behandlung oder Prophylaxe eines Leidens, wie es in irgendeinem der Ansprüche 3 bis 8 definiert ist.

12. Salz, wie es in irgendeinem der Ansprüche 9 bis 11 beansprucht wird, das kristallin ist.

13. Pharmazeutische Zusammensetzung aus einem Salz, wie es in irgendeinem der Ansprüche 9 bis 12 beansprucht wird, zusammen mit einem pharmazeutisch annehmbaren Träger.

Revendications

1. Utilisation d'un sel de magnésium de (-)-5-méthoxy-2-[[(4-méthoxy-3,5-diméthyl-2-pyridinyl)-méthyl]sulfiny]-1H-benzimidazole ((-)-oméprazole), ayant une pureté optique à excès énantiomérique (e.e.) ≥ à 99,8 %, pour la fabrication d'un médicament pour l'inhibition de la sécrétion d'acide gastrique.

2. Utilisation selon la revendication 1, dans laquelle le sel est cristallin.

3. Utilisation selon la revendication 1 ou la revendication 2, dans laquelle le médicament est pour le traitement d'une maladie liée à l'acide gastrique et/ou d'une maladie inflammatoire gastro-intestinale.

4. Utilisation selon la revendication 3, dans laquelle la maladie est un ulcère gastrique, un ulcère duodénal, une oesophagite par reflux ou une gastrite.

5. Utilisation selon la revendication 4, dans laquelle la maladie est une oesophagite par reflux.

6. Utilisation selon la revendication 1 ou la revendication 2, dans laquelle le patient est sous thérapie par AINS, a un gastrinome et/ou a un saignement gastro-intestinal supérieur aigu.

7. Utilisation selon la revendication 1 ou la revendication 2, dans laquelle le médicament est pour le traitement d'un patient dans une situation de soins intensifs et/ou doit être utilisé en pré- et postopératoire pour prévenir une aspiration d'acide et une ulcération de stress.

8. Utilisation selon la revendication 1 ou la revendications 2, dans laquelle le médicament est utilisé dans le traitement d'une infection à *Helicobacter*.

9. Sel de magnésium de (-)-5-méthoxy-2-[[(4-méthoxy-3,5-diméthyl-2-pyridinyl)méthyl]sulfinyl]-1H-benzimidazole ((-)-oméprazole) ayant une pureté optique à excès énantiomérique (e.e.) ≥ à 99,8 %.

10. Sel selon la revendication 9, pour une utilisation en thérapie.

11. Sel selon la revendication 10, pour une utilisation dans le traitement ou la prophylaxie d'une affection telle que définie dans l'une quelconque des revendications 3 à 8.

12. Sel selon l'une quelconque des revendications 9 à 11, qui est cristallin.

13. Composition pharmaceutique d'un sel selon l'une quelconque des revendications 9 à 12, conjointement avec un véhicule pharmaceutiquement acceptable.

REFERENCES CITED IN THE DESCRIPTION

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Patent documents cited in the description

- EP 5129 A **[0002]**
- EP 124495 A **[0002]**
- DE 4035455 **[0003]**

Non-patent literature cited in the description

- *J. Chromatography,* 1990, vol. 532, 305-19 **[0003]**